DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
1431 Harbor Bay Parkway Alameda, CA 94502-7070 (510) 337-6700 Fax:(510) 337-6702 Industry Information: www.fda.gov/oc/industry	09/03/2013 - 09/10/2013* FEI NUMBER 3006365166

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Daniel R. Wills, General Business Manager

FIRM NAME	STREET ADDRESS
Grandpa's Compounding Pharmacy, Inc.	7563 Green Valley Rd
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Placerville, CA 95667-3917	Producer of Sterile Products

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

Aseptic processing areas are deficient regarding air supply that is filtered through high-efficiency particulate air filters under positive pressure.

Specifically,

1. The aseptic operations for sterile injectable drugs are performed within a horizontal air flow hood. The following observations pertain to the air handling system, the ISO-5 classified air flow hood, the ISO-7 area, and the ISO-8 ante room.

   a. As per the "Clean Room and Laminar Airflow Hood Certification" document SOP No. 3.3.30, dated Jun 19, 2013 establishes that the certification is performed every (b) (4). However, there is no raw data to support the ISO-5 classification and the air flow hood is labeled and identified as Class 7. The procedure is silent with respect to performing air flow pattern (aka smoke study) evaluations;

   b. There are no records that describe (e.g., written description and/or installation diagram) the air handling system that is used to provide air for the ISO-7 and ISO-8 classified areas. There is no equipment qualification and/or validation of the air handling system. Please note that the ISO-5 classified air flow hood draws air from the ISO-7 room. In addition;

   c. The air supply for the clean room is distributed via a (b) (4) [approximate (b) (4) (b) (4)(b) (4) (b) (4)(b) (4) When asked the General Manager explained that he did not know if the (b) (4) contains HEPA filter(s); and,

   d. A section of the (b) (4) (i.e., the joining edge where the top and side (b) (4) (b) (4) meet) is partially secured with gray color duct tape and parts of the top section of the box

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	Ashar P. Parikh, Investigator Thomas J. Arista, Investigator	09/10/2013

is not completely secured such that air could be felt escaping from the edge of the [redacted] (b) (4) (b) ;

e. There is a small [redacted] (b) (4) air conditioner (e.g., small window type unit) located on the bottom (approximately 6-8" off the floor) right hand side of the air flow hood. The General Manager confirmed that is air conditioner is used *"to circulate the air"* within the clean room. There is no record to document the installation and qualification of the small window type air conditioner and it is unknown if the air conditioner draws air from the outside of the building and enters into the ISO-7 classified area; and,

f. There is no record or manner with which the air pressure can be measured and/or monitored between the clean room, the ISO-7 and ISO-8 support rooms. Rather, as confirmed by the General Manger, air pressure is determined by *"visually observing"* movement of the plastic curtains that are used as a physical barrier between the rooms. Furthermore, the "Positive Pressure Monitoring" document SOP No. 3.3.10 dated Jun 19, 2013, establishes the standard practice as follows, *"Positive Pressure is obtained when the plastic cover is pushed out at floor level."*

2. The "General Aseptic Procedures Used at a Laminar Airflow Workbench" document SOP No. 5.6.33, dated Jun 19, 2013, establish if the hood blower is not continuously used, to turn the hood off. Prior to performing the aseptic operations the hood is turned on [redacted] (b) (4) (b) (4) " Irrespective of the aforementioned [redacted] (b) (4), there is no Non-Viable Particle (NVP) measurements taken during dynamic operations, i.e., when technicians are performing the aseptic operations within the ISO-5 hood and the ISO-7 room. The NVP level during the aseptic operations performed for the sterile drugs is unknown. In addition;

a. There has been no air flow pattern (e.g., smoke study) evaluation performed to determine the acceptability of the horizontal air flow, that is, the air flow is not compromised (e.g., air turbulence/air eddies) during the aseptic operations that are performed in the ISO-5 area. The General Manager confirmed that air flow pattern evaluations have not been performed by the contractor. Note: The incoming air for the ISO-7 room is via the ceiling air vent above the horizontal air flow cabinet and the LG small air conditioner wall unit that is used to circulate the air. In addition;

b. There has been no air flow pattern evaluation to determine that the personnel activities and

manual transfer of materials between the ISO-8 and ISO-7 areas do not negatively affect the air movement and air cascade i.e., air moving outward from the ISO-7 area towards the ISO-8 ante room and not the converse.

OBSERVATION 2

Clothing of personnel engaged in the manufacturing and processing of drug products is not appropriate for the duties they perform.

Specifically, prior to entry into the clean room and as a requisite for performing the aseptic operations, technicians are required to don (over their laboratory attire) disposable blue color smock with knit cuffs, mouth and nose cover, hair cover, as well as, shoe covers. Note: the blue color smock is tied from the back similar to a hospital gown. Excluding the [redacted] (b) (4) sterilized gloves none of the personnel gowning attire is sterile or made of non-particle shedding material. After we pointed out that the use of the non-sterile gowning attire, the PIC stated that *"this is news to me"*.

In addition while carrying a small envelope/package of sterile gloves, personnel enter into the clean room, i.e., backing into the plastic barrier curtains that separate the ISO-7 and ISO-8 rooms. As previously noted above, the blue color scrubs are similar to a hospital gown and as such the uncovered laboratory attire come in direct contact with the plastic curtains. Once personnel are in the clean room, we observed personnel donning the sterile gloves inside the ISO-5 horizontal air flow hood. We observed exposed skin during the aseptic operations including the operators forehead, eyes, cheeks, wrists, and forearms.

OBSERVATION 3

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established and written.

Specifically,

a. The "Use of Ante Room and Clean Room" document SOP No. 3.3.15 approved Jun 19, 2013 establish that "Proper attire and washing must be in place prior to entering the Clean Room. Proper aseptic technique must be strictly adhered to at all times when working in Laminar Flow Hood." However, the procedure is silent with respect to establishing the use of sterile

attire or non-particle shedding gowning attire;

b. After donning of the requisite gowning attire that is required for aseptic operations, personnel are required to wash their hands and arms (up to their elbows) with a scrub brush and tap water that is filtered with a [redacted] (b) (4) faucet filter; hands and arms are dried with a hand wipe and subsequently air dried by placing arms and hands up the air;

c. The "Capping Filled Vials" document SOP No. 5.6.52 dated Jun 19, 2013, establishes after the septum is properly placed on the vial to "Place the aluminum rim over the septum on the vial. Seal vial with Crimper before removing from the Hood." Despite the establishment of the aforementioned procedure, we observed a technician placing the aluminum rim and sealing the over seal in the ISO-7 area, which is not consistent with the established procedure.

d. The vial stoppers (septum) are subject to [redacted] (b) (4) sterilization. However, there has been no evaluation and analysis to determine the absence of Bacterial Endotoxin for the vial stoppers.

Also, the Environmental Monitoring (EM) Program consists of obtaining surface and air samples on a [redacted] (b) (4) basis from the interior of the air flow hood as per the "Environmental Testing for Laminar Flow Hood - EnviroTest" document No. 3.3.35, dated Jun 19, 2013. The incubation temperature can be either at [redacted] (b) (4). However, there is no record to document the time and temperature of the EM samples. In addition;

a. Personnel monitoring is performed via [redacted] (b) (4) prior to aseptic operations. However, there are no other EM samples taken to evaluate the microbial presence on personnel performing the aseptic operations;
b. Other than the [redacted] (b) (4) sampling (i.e. [redacted] (b) (4)), there is no other EM samples taken to determine the microbial levels within the classified areas i.e., ISO-5 hood, ISO-7 & ISO8 ante room, or for the plastic barrier curtains that separate the classified areas
c. There is no evaluation performed to determine the microbial trending of the classified areas or for the personnel monitoring and there is no data to support the [redacted] (b) (4) sampling is sufficient to adequately evaluate the microbiological presence of the classified areas.
d. No EM sample taken of [redacted] (b) (4) filter tap water to determine the level of bacteria and bacterial endotoxin.

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OBSERVATION 4

Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use.

Specifically, tap water (sink in the ISO-8 ante room is filtered via the use of a [redacted] (b) (4) faucet filter) is used to wash personnel hands and arms as well as to clean and wash amber color vials that are used for aseptically filled sterile drug commodities. The filter manufacturer submits that the *"faucet filtration system is not intended to purify water"*. Furthermore, the faucet system is not designed, or intended, for the removal and/or retention of bacterial endotoxin. When asked if the [redacted] (b) (4) faucet filter was periodically removed and replaced, the technician explained that she believed the filter is replaced however there is no record to document the practice.

In addition, the [redacted] (b) (4) is used to dry heat sterilizer and used to depyrogenate utensils. The [redacted] (b) (4) is not designed, or intended, as a dry heat sterilizer or as depyrogenation equipment.

OBSERVATION 5

Equipment and utensils are not maintained at appropriate intervals to prevent malfunctions that would alter the safety, identity, strength, quality or purity of the drug product.

Specifically, a [redacted] (b) (4) is used to [redacted] (b) (4) sterilize utensils (forceps), glass vials and vial stoppers (septum) and gloves that are used during the aseptic operations for the sterile injectable drug commodities. The Pharmacist confirmed that there is no record to document equipment qualification and no record to document the validation of the sterilization process. In addition;

a. A combination biological indictor (BI) consisting of *Bacillus atropheus* and *Geobacillus stearothermophilus* is used to determine if sterilization is achieved. There is no specific D-value or microbial population described. The BIs are required to be incubated at [redacted] (b) (4) (b) (4) However, there is no record to document that the requisite time and temperature requirements are maintained to assure that the BIs are appropriately incubated;
b. There is no record to document the equipment qualification and no record to document the validation of the [redacted] (b) (4) sterilization and depyrogenation processes. The "[redacted] (b) (4) Depyrogenation of Glassware and Metalware" document SOP No. 5.6.23 dated Jun 19, 2013,

establishes that "Care must be taken in loading the [(b) (4)]. *Note: Overloading should be avoided."* There is no record to document the load configuration of the [(b) (4)]. Similarly, there is no load configuration for the [(b) (4)] sterilizer.

Specifically, Sterile Room Procedures 5.6.40 dated Jun 19, 2013, #13 specifically states to "Clean the surfaces of the direct compounding environment with purified water at the beginning of each compounding activity session and after liquids are spilled, to remove water soluble residues. Note: Immediately thereafter, the same surfaces should be sanitized with [(b) (4)] or other effective antimicrobial agents, using a nonlinting wipe." However, the [(b) (4)] and the [(b) (4)] antimicrobial agent are not sterile and the [(b) (4)] is not a sporicidal agent.

OBSERVATION 6

Records of the calibration checks of automatic, mechanical or electronic equipment, including computers or related systems are not maintained.

Specifically, there is no record to document that the monitoring devices used to obtain the sterilization time, temperature and pressures are calibrated to a reference standard.

a. There are no records to document the calibration of the monitoring devices for the [(b) (4)] sterilization and depyrogenation [(b) (4)] noted below. The [(b) (4)] Sterilizing [(b) (4)]-Use" document SOP No. 3.3.37 dated Jun 19, 2013, establishes, ***"CAUTION: Do not depend upon the [(b) (4)] to set the temperature."***

b. A [(b) (4)] integrity tests is performed for the [(b) (4)] post use of the sterile [(b) (4)] performed during the aseptic operations. There is no standard procedure to describe how to perform the integrity tests and there is no record to document that the pressure gauge is calibrated to a reference standard.

OBSERVATION 7

Laboratory records do not include a statement of the location of data that establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested.

Specifically the "Sterility / Endotoxin Testing" document SOP No. 9.1.30, date 5 June 2013, is

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established to address the Sterile Injectable Compounding Quality Assurance and Process Validation, which includes Sterility Test and Pyrogen tests via the use, for example, of [redacted] (b) (4) for all but suspensions and [redacted] (b) (4) for sterile suspensions and [redacted] (b) (4) test, respectively. The following observations concern the Sterility and Bacterial Endotoxin testing, that is;

a. The [redacted] (b) (4) is used to determine that the material (e.g., drug products) under test is not contaminated. After checking with the [redacted] (b) (4) manufacturer the General Manager confirmed that the [redacted] (b) (4) is specifically for suspensions and emulsions. The microbial contamination tester is NOT intended for other dosage forms/commodities (e.g., liquid/solutions); and the [redacted] (b) (4) (b) (4)(b) (4)(b) (4) is not the official test and has not been shown to be reliably equivalent to the United States Pharmacopeia <71> Sterility Test;

b. The [redacted] (b) (4) requires an incubation temperature [redacted] (b) (4) (b) and [redacted] (b) (4) The microbial tester is not placed inside an incubator. Rather the microbial tester is placed in a small plastic basket that sits on top of a small incubator. And, there is no record to document the requisite time and temperature and the inversion requirements;

c. The bacterial endotoxin test is performed via the use of the [redacted] (b) (4) (b) (4)(b) (4)(b) (4)(b) (4)(b) (4) which is a gel-clot method of analysis. The method states that "Some ingredients interfere with the [redacted] (b) (4) test. The [redacted] (b) (4) may not provide reliable results when attempting to detect excessive endotoxin in these materials: Suspension, emulsions, phenols, lipids, chelators, antibiotics, surfactants, alcohol's with a final concentration (after dilution) or greater than 0.1%...)" There is no study/evaluation to determine that the materials under tests do not *"interfere with the* [redacted] (b) (4) *test"*;

d. The [redacted] (b) (4) tests require that [redacted] (b) (4) (b) (4)(b) (4)(b) (4)(b) (4)(b) (4) However, there is no record to document that the requisite incubation time and temperature are achieved; The [redacted] (b) (4) assay vials are placed inside an incubator that is located next to the ISO-8 anti-room entry way (a high personnel and material movement area);

e. There is not record to document that the Positive Control Vial had a "firm" gel clot which confirms that "*the assay was performed properly and that the dilution of the test sample does*

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not interfere with the accurate detection of gram-negative endotoxin"

f. The Pharmacist explained the inversion of the assay vials, which included a brief demonstration that is inversion at approximately 90 degrees, which is not consistent with the required manual (b) (4) degree inversion to assure that the gel-clot is not compromised i.e., *"firm" gel which remains intact when the vial is inverted"*

OBSERVATION 8

Individuals responsible for supervising the manufacture and processing of a drug product lack the education, training, and experience to perform their assigned functions in such a manner as to assure the drug product has the safety, identity, strength, quality and purity that it purports or is represented to possess.

9/10/13

Specifically, the following observations document that the Pharmacists, Pharmacist-In-Charge (PIC) and the General Manager do not have the training and experience to provide assurance with respect to basic requirements needed in support of aseptic operations and sterile drugs. This would include, for example, the support utilities (HVAC, Water), personnel aseptic practices and procedures, Quality Control tests and laboratory equipment that are used in support of the aseptic operations.

In addition, the "Supervising Pharmacist Responsibilities/Pharmacist-In-Charge (PIC)" document SOP No. 2.35, dated Jun 19, 2013, establishes the responsibilities, that include for example, "PIC and/or Supervising Pharmacist reports to the General Manager on overall effectiveness of employees individually and as a whole. Also keeps the General Manger informed of all legal and quality control issues that affect the operations of the store." The procedure is silent with respect to assessing the support utilities, personnel aseptic practices and procedures, Quality Control tests and laboratory equipment used in support of the aseptic operations.

OBSERVATION 9

Equipment surfaces that contact drug products are reactive, additive or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

Specifically, peeling (white color) paint is observed inside and outside the horizontal air flow hood as well as what appears to be "rust" like material inside of and on the exterior surfaces of the hood; When asked the PIC confirmed that he was unaware of the rust-like material.

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OBSERVATION 10

Buildings used in the manufacturing and processing of a drug product are not maintained in a good state of repair.

Specifically, a water stain was observed on the ceiling of the ISO-8 ante room that leads into the clean room. When asked, the PIC confirmed that he was unaware of the water stain. No evaluation has been performed to determine the source or cause that generated the water stain.

*** DATES OF INSPECTION:**
09/03/2013(Tue), 09/04/2013(Wed), 09/06/2013(Fri), 09/10/2013(Tue)

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